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Considering the biology of late recurrences in selecting patients for extended endocrine therapy in breast cancer

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ABSTRACT

Extended endocrine therapy can reduce recurrences occurring more than 5 years after diagnosis (late recurrences) in estrogen receptor (ER)-positive breast cancer. Given the side effects of endocrine therapy, optimal patient selection for extended treatment is crucial. Enhanced understanding of late recurrence biology could optimize patient selection in this setting. We therefore summarized the current knowledge of late recurrence biology, clinical trials on extended endocrine therapy, and tools for predicting late recurrence and benefit from treatment extension. Extending 5 years of tamoxifen therapy with 5 years of tamoxifen or an aromatase inhibitor (AI) reduces late recurrence risk by 2–5%, but results of extending AI-based therapy are inconsistent. Although several clinicopathological parameters and multigene assays are prognostic for late recurrence, selection tools predicting benefit from extended endocrine therapy are sparse. Therefore, we additionally performed a pooled analysis using 2231 mRNA profiles of patients with ER-positive/human epidermal growth factor receptor 2-negative breast cancer. Gene Set Enrichment Analysis was applied on genes ranked according to their association with early and late recurrence risk. Higher expression of estrogen-responsive genes was associated with a high recurrence risk beyond 5 years after diagnosis when patients had received no systemic therapy. Although 5 years of endocrine therapy reduced this risk, this effect disappeared after treatment cessation. This suggests that late recurrences of tumors with high expression of estrogen-responsive genes are likely ER-driven. Long-term intervention in this pathway by means of extended endocrine therapy might reduce late recurrences in patients with tumors showing high expression of estrogen-responsive genes.

Introduction

Endocrine therapy in patients with estrogen receptor (ER)-positive breast cancer has clearly improved patient outcomes. Nevertheless, at least 20–25% of patients experience breast cancer recurrence at some point, which might present as locoregional relapse, distant recurrence or second primary breast cancer [1,2]. Half of these recurrences are late recurrences occurring more than 5 years after diagnosis [1]. Even for patients with T1N0, ER-positive tumors who received 5 years of endocrine therapy, the cumulative distant recurrence rate 5–20 years after diagnosis is still 13% [2].

Several trials have shown a reduced late recurrence risk with extended endocrine therapy beyond 5 years [3–7]. However, absolute benefits of this extension are modest, yielding only a 2–5% reduction in late recurrence. As endocrine therapy can be accompanied by severe side effects, identification of patients who will benefit most from extended treatment is crucial. Multiple tools such as web-based risk calculators and multigene assays have been developed to estimate the recurrence risk in ER-positive breast cancer [8,9]. Although some of these tools are also prognostic for late recurrence, not all patients with a high estimated risk will benefit from extended endocrine therapy.

Gaining insight into late recurrence biology could optimize patient selection for extended endocrine therapy. Therefore, we reviewed the current knowledge of late recurrence biology, clinical trials on extended endocrine therapy, and tools for predicting late recurrence and benefit from treatment extension. Additionally, we performed a pooled analysis using 2231 mRNA profiles of primary ER-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancers to identify biological pathways associated with an increased early or late recurrence risk in patients that received no systemic treatment and in

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patients that only received 5 years of endocrine therapy.

Current knowledge of late recurrence biology

Early distant recurrences, but not late recurrences, appear to be the result of a continuous-growth model where the steps of the invasion-metastasis cascade are continuous [10]. A retrospective study including 1173 patients with breast cancer regardless of ER or HER2 status, treated with mastectomy alone, showed a two-peak incidence: at 18 months and at around 60 months after surgery for local and distant recurrences [11]. This two-peak incidence, which was also observed in other studies, might be a result of tumor dormancy [12–16].

Two types of tumor dormancy have been distinguished. In tumor mass dormancy, expansion of a micrometastatic lesion is inhibited as proliferating and dying tumor cells balance each other. Underlying mechanisms for tumor mass dormancy include (i) angiogenic dormancy, where the size of the lesion is kept constant because of a limited blood supply, and (ii) immune-mediated dormancy, where a low number of proliferating tumor cells is maintained through a continuous cytotoxic activity [17]. In cellular dormancy, single disseminated tumor cells (DTCs) reach a quiescent state by arresting in the G0-G1 cell cycle phase, which likely results from their inability to adapt to a new microenvironment after surviving dissemination [17,18].

Knowledge of mechanisms responsible for the reactivation of dormant micrometastatic lesions or dormant DTCs is limited. This reactivation could be regulated mainly through signals from the tumor microenvironment, including cues in the extracellular matrix, the immune microenvironment and angiogenetic factors [17,19–21].

Extending tamoxifen treatment beyond 5 years

All trials assessing extended endocrine therapy have been performed in patients regardless of HER2 status. Recurrences were defined as locoregional relapses, distant recurrences or second primary breast cancers. Disease-free survival (DFS) was defined as time from diagnosis to recurrence, second primary malignancy or death unless stated otherwise.

The first trials evaluating extended tamoxifen treatment included small numbers of patients with hormone receptor-positive and hormone receptor-negative tumors [22,23]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial was the first study to randomize 1152 patients with ER-positive disease who completed

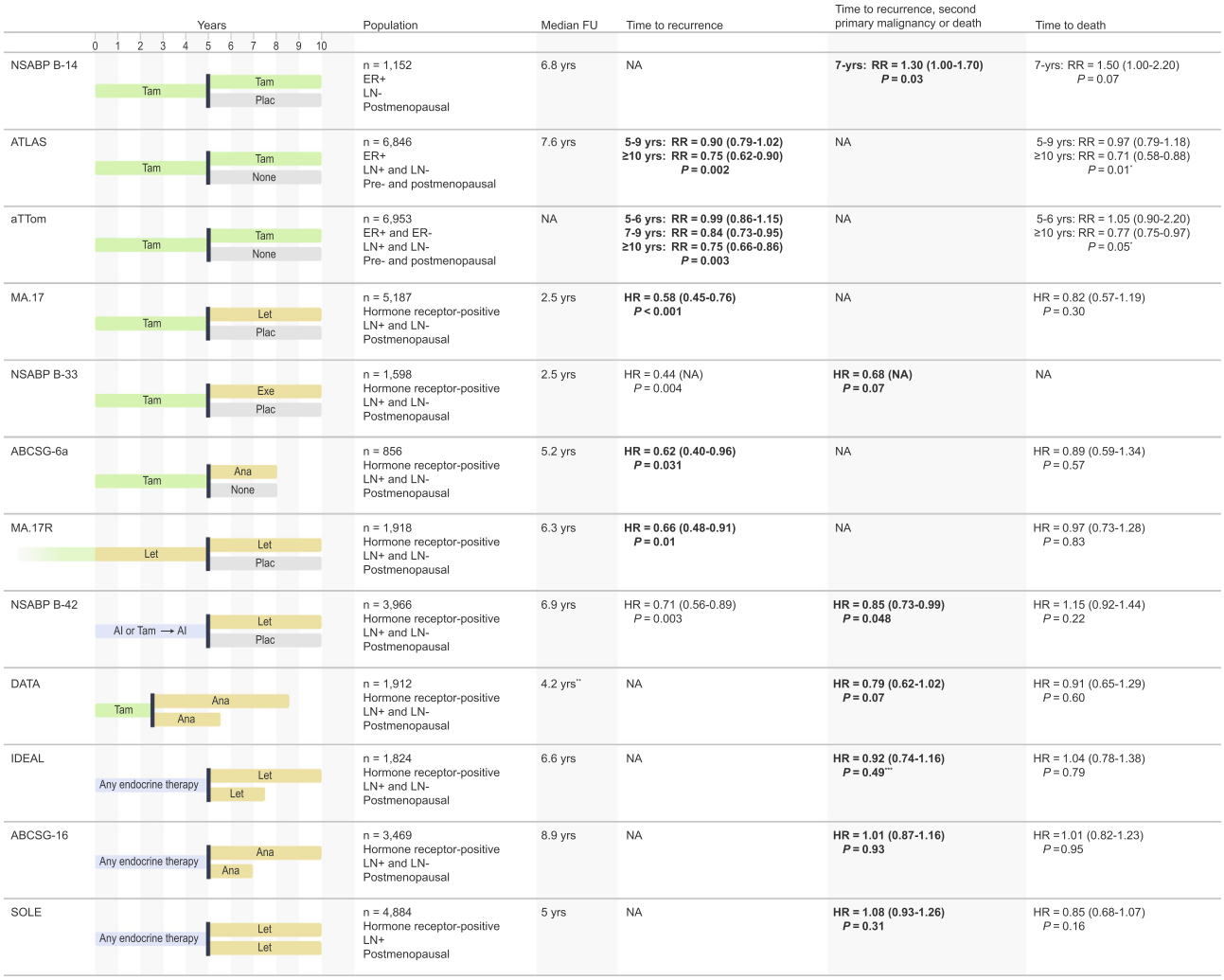

Fig. 1. Clinical trials on extending endocrine therapy beyond 5 years. Recurrences were defined as locoregional relapse, distant recurrence or second primary breast cancer. Median follow-up times were calculated from time of randomization onwards. The primary endpoint of each trial is displayed in bold. Relative risks and hazard ratios are presented with corresponding 95% confidence intervals. A relative risk or hazard ratio of greater than 1 represents a greater risk for the treatment arm (upper bar) compared to the control arm (lower bar) in each trial. *Breast cancer-specific death only. **Adapted median follow-up starting at 3 years from randomization. ***Did not include primary malignancies. AI, aromatase inhibitor; Ana, anastrozole; ER, oestrogen receptor; Exe, exemestane; FU, follow-up; HR, hazard ratio; Let, letrozole; LN, lymph node; NA, not available; Plac, placebo; RR, relative risk; Tam, tamoxifen; yrs, years.

5 years of tamoxifen, to another 5 years of tamoxifen or placebo (Fig. 1) [24]. This study, which only included patients with node-negative disease, was terminated early after interim analyses indicated that a statistically significant benefit was unlikely [25]. With a median follow-up of 6.8 years, the 7-year DFS was 78% in patients receiving extended tamoxifen versus 82% in patients receiving placebo.

More recently, the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial randomized 6846 patients with ER-positive disease who completed 5 years of tamoxifen to another 5 years of tamoxifen or no further treatment [3]. With a median follow-up of 7.6 years after randomization, a 3.7% difference was observed in the cumulative recurrence rate in years 5–14 after diagnosis in favor of the extended tamoxifen arm. Also, a 2.8% reduction in breast cancer mortality was seen in patients receiving 10 years of tamoxifen. Similar results were observed in the adjuvant Tamoxifen—To offer more? (aTTom) trial, which included 6953 patients of which most had an unknown tumor ER status [4].

Extended tamoxifen treatment seems to be reasonably tolerated. In ATLAS, 84% of patients who received extended tamoxifen and remained disease-free 2 years after randomization were still on treatment. However, patients were preselected for good tamoxifen tolerance, so patient adherence to extended tamoxifen is likely somewhat lower than reported in ATLAS. It is known that 5 years of tamoxifen increases the risk for endometrial cancer and pulmonary embolism [26]. In ATLAS, the incidence of endometrial cancer and pulmonary embolism approximately doubled when patients received extended tamoxifen. The cumulative endometrial cancer rate increased by 1.5% to 3.1% in years 5–14 after diagnosis.

Based on the ATLAS and aTTom trials, current guidelines recommend that all patients receiving 5 years of tamoxifen should be offered the option to extend tamoxifen to 10 years [27].

Aromatase inhibitor-based treatment after 5 years of tamoxifen

Trials evaluating extended treatment with aromatase inhibitors (AIs) have included only postmenopausal patients with hormone receptor-positive disease.

The MA.17 trial included 5187 patients who completed 5 years of tamoxifen and randomized these patients to 5 years of letrozole or placebo (Fig. 1). This study was prematurely unblinded when interim analyses showed that letrozole reduced recurrence risk [28]. A 4.6% lower 4-year recurrence rate was seen in patients receiving letrozole compared to placebo [5]. Although no significant difference in overall survival (OS) was found initially, analysis adjusting for treatment crossover with a median follow-up of 5.3 years revealed that letrozole prolonged OS (hazard ratio [HR] 0.61, 95% confidence interval [CI] 0.52–0.71) [29]. These findings resulted in the premature closure of the NSABP B-33 trial, where 1598 patients after 5 years of tamoxifen were randomized to 5 years of exemestane or placebo [30]. With a median follow-up of 2.5 years after randomization, a 2% difference was seen in the 4-year recurrence rate in favor of the exemestane arm. The Austrian Breast and Colorectal Cancer Study Group (ABCSG) Trial 6a randomized 856 patients who received 5 years of tamoxifen to 3 years of anastrozole or no further treatment [6]. The cumulative recurrence rate 5 years after randomization was 12.2% for patients receiving no further treatment and 7.8% for patients receiving anastrozole. No significant difference in OS was observed.

Side effects of 5 years of AI-based treatment include arthralgia, hot flushes, cardiovascular disease and a decrease in bone mineral density resulting in osteoporosis or bone fractures [31–34]. None of these trials reported an increased bone fracture incidence following extended treatment with an AI. MA.17 reported a 2.1% increase in newly diagnosed osteoporosis in patients receiving extended treatment. Hot flushes, arthralgia and myalgia were also more common. In NSABP B-33, 3% more grade 3 side effects, mainly arthralgia, fatigue and bone pain, were seen in patients receiving extended treatment. In ABCSG Trial 6a, 11.6% of patients receiving extended anastrozole withdrew prematurely because of adverse events.

Extending treatment with an AI after 5 years of tamoxifen reduces late recurrence risk, but is accompanied by an increase in side effects, mainly bone-related, and arthralgia. Current guidelines recommend that all postmenopausal patients who have received 5 years of tamoxifen should be offered the option to extend treatment with 5 years of an AI [27].

Extending aromatase inhibitor-based treatment beyond 5 years

The MA.17R trial included 1918 patients who completed 5 years of letrozole, preceded in 80% of patients by 5 years of tamoxifen (Fig. 1). Patients were randomized to letrozole for another 5 years or placebo [7]. With a median follow-up of 6.3 years after randomization, 95% of patients who received letrozole were recurrence-free at 5 years versus 91% of patients who received placebo. This difference was mainly driven by a reduction in contralateral breast cancers (HR 0.42, 95% CI 0.22–0.81). In the NSABP B-42 trial, 3966 patients who received an AI or tamoxifen followed by an AI for 5 years were randomized to 5 years of letrozole or placebo [35]. As there was no significant difference in DFS, this trial did not meet its primary endpoint; the median follow-up was 6.9 years after randomization. Extended letrozole did result in a 3.3% lower 7-year recurrence rate and a 1.9% lower 7-year distant recurrence rate. The DATA trial randomized 1912 patients who completed 2–3 years of tamoxifen to 3 or 6 years of anastrozole [36]. Follow-up started 3 years after randomization. No significant difference in DFS was observed with a median follow-up of 4.2 years. However, post-hoc subset analysis showed that extended anastrozole improved DFS in patients with ER-positive/progesterone receptor (PR)-positive, node-positive disease (HR 0.64, 95% CI 0.46–0.89), which was even more evident when patients also had a large tumor size (HR 0.53, 95% CI 0.35–0.82). Another trial evaluating the effect of 2–3 versus 5 years of letrozole in patients who completed 2–3 years of tamoxifen is currently ongoing (NCT01064635).

Several trials compared different durations of extended AI-based treatment beyond 5 years. In the Investigation on the Duration of Extended Adjuvant Letrozole treatment (IDEAL) trial, after 5 years of any endocrine therapy 1824 patients were randomized to 2.5 or 5 years of letrozole [37]. No significant difference in DFS, in which second primary malignancies were not considered events, was observed with a median follow-up of 6.6 years after randomization. However, 5 years of letrozole did result in a reduction of second primary breast cancers (HR 0.39, 95% CI 0.19–0.81). The ABCSG-16 trial randomized 3469 patients after 5 years of any endocrine therapy to 2 or 5 years of anastrozole [38]. With a median follow-up of 8.9 years after randomization, no significant difference was found in DFS or OS. Finally, the Study of Letrozole Extension (SOLE) trial randomized 4884 patients with node-positive disease after 5 years of any endocrine therapy to 5 years of continuous or intermittent letrozole [39]. With a median follow-up of 5 years after randomization, no significant difference was observed in DFS or OS.

In the MA.17R trial, the incidences of new-onset osteoporosis and bone fractures were both 5% higher in patients receiving extended letrozole. In contrast, NSABP B-42 and DATA did not report a significant difference in bone fractures. In DATA, an increased incidence of arthralgia and myalgia was seen in patients receiving extended treatment, of which 24% withdrew because of side effects. Furthermore, a meta-analysis of seven clinical trials comprising 16,349 patients showed that extended AI treatment after 5 years of either tamoxifen or AI-based therapy results in an increased risk for cardiovascular disease and fractures [40]. As patients were preselected for good tolerance of endocrine therapy, these data indicate that treatment extension itself does inflict additional toxicity. In both IDEAL and ABCSG-16, around 60% of patients receiving 5 years of extended treatment completed treatment.

In summary, no evidence currently indicates that extending AI-

based treatment beyond 5 years reduces late recurrence risk in an unselected population of patients with ER-positive breast cancer. Subset analyses indicate that patients with ER-positive/PR-positive, node-positive disease might benefit from extended AI-based treatment. However, these assumptions need to be interpreted with caution as the number of events in these analyses were low.

Tools for predicting late recurrence and benefit from extended endocrine therapy

Several tools that are currently used to predict recurrence risk in ER-positive breast cancer also have prognostic value for late recurrence. A meta-analysis including 62,923 patients showed that T and N status were the strongest determinants for late distant recurrence after 5 years of endocrine therapy [2]. This has also been demonstrated by several smaller studies [41,42]. Web-based risk calculators such as Adjuvant!Online, PREDICT and CancerMath also provide information on long-term recurrence risk by incorporating clinicopathological parameters and epidemiological data (Table 1) [8,43,44].

Multigene assays have also been assessed in the context of late recurrence (Table 2). Oncotype DX is a 21-gene assay measured at mRNA level that identifies patients with early-stage, node-negative disease who are likely to benefit from adjuvant chemotherapy [9]. Prosigna is a mRNA-based 50-gene assay incorporating genes from the PAM50 algorithm for intrinsic subtype classification; it estimates the 10-year distant recurrence risk [45,46]. IHC4 is a prognostic score derived from immunohistochemical staining levels of ER, PR, HER2 and Ki67 [47]. The Breast Cancer Index combines two independent mRNA biomarkers, HOXB13/IL17BR (H/I) and the Molecular Grade Index, to calculate distant recurrence risk in patients with node-negative disease [48,49]. Finally, EndoPredict is a RNA-based 11-gene assay composed of proliferative and ER-related genes, which can be combined with tumor size and nodal status, resulting in the EPclin score [50]. In several patient subsets of the TransATAC trial, where patients with ER-positive disease received 5 years of endocrine therapy, Prosigna, Breast Cancer Index and EndoPredict/EPclin predicted late distant recurrence risk independent of age, tumor size, grade, nodal status and treatment (Table 3). In contrast, Oncotype DX and IHC4 were of little or no prognostic value [42,51,52]. In a comparison of all assays in 689 patients from TransATAC, Prosigna was the strongest independent predictor for late recurrence in node-negative breast cancer, while EPclin was the strongest in patients with node-positive disease [53]. The independent prognostic value for late distant recurrence of Prosigna, Breast Cancer Index and EndoPredict has also been demonstrated in other patient cohorts [54–58].

ER-related gene expression has also been studied in the context of late recurrence. A study including 1242 patients with ER-positive breast cancer treated with 5 years of tamoxifen showed that, independent of age, T stage, nodal status, grade and HER2 status, tumors with a combined high proliferation and high ER-related score had the greatest increase in distant recurrence risk after 5 years of tamoxifen [59]. Also, among patients with highly proliferative tumors treated with neoadjuvant letrozole, a 100% (11/11) clinical response rate was seen in tumors with high ER-related gene expression, compared to 47% (7/15) in case of low ER-related gene expression. In 1125 patients who received 5 years of endocrine therapy in TransATAC, tumors with low ESR1 mRNA expression showed a steady distant recurrence rate across 10 years after diagnosis, while high ESR1 expression was associated with a lower early distant recurrence risk but an increased late distant recurrence risk [60]. Furthermore, Oncotype DX was prognostic for late distant recurrence in case of high tumor ESR1 mRNA expression in chemotherapy and tamoxifen-treated patients and patients treated with tamoxifen only, while this was not the case for low ESR1 expression [61].

Recently, the Clinical Treatment Score post-5 years (CTS5) was developed specifically to predict late distant recurrences by incorporating

Table 1
Web-based tools for long-term risk in estrogen receptor-positive breast cancer.

Web-Based Tool	Assessment	Conceptual Basis	Required information	Utility
Adjuvant!Online	Risk of recurrence and death at 10 years	Estimated of prognosis based on SEER data and estimated of efficacy of adjuvant therapy based on EBCTCG data	Patient age at diagnosis, patient comorbidities, tumor size, ER status and number of lymph nodes involved	Estimate realistic benefit of adjuvant therapy
PREDICT	5-year and 10-year survival risk	Data from East Anglia Cancer Registration and Information Center	Patient age at diagnosis, mode of detection, tumor size, tumor grade, ER status, HER2 status, Ki67 status, chemotherapy regimen	Estimate the effect of endocrine therapy and chemotherapy
CancerMath	15-year mortality risk	SNAP (size, nodes, prognostic markers) for integrating prognostic factors to estimate mortality risk NIH population data to estimate the risk of non-breast cancer death	Patient age at diagnosis, tumor size, number of lymph nodes involved, ER status, PR status, HER2 status, histological type, grade, treatment regimen	Estimate 15-year mortality risk and impact of endocrine therapy and chemotherapy

EBCTCG, Early Breast Cancer Trialists' Collaborative Group; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NIH, National Institutes of Health; PR, progesterone receptor; SEER, Surveillance, Epidemiology, and End Results.

Table 2
Multigene assays evaluated to predict late recurrence risk in estrogen receptor-positive breast cancer.

Assay	Details	Technology	Application	Output
Oncotype DX [9]	16 cancer-related genes and 5 reference genes	mRNA quantification by RT-PCR	Prediction of 10-year recurrence risk in patients with ER + /HER2-, LN- breast cancer	Continuous recurrence score & risk classification (low, intermediate, high)
Prosigna [45,46]	50 genes used in the PAM50 algorithm for intrinsic molecular subtype classification	mRNA quantification by RT-PCR	Prediction of 10-year recurrence risk in patients with ER + /HER2-, LN + /LN- breast cancer	Continuous recurrence score & risk classification (low, intermediate, high)
IHC4 [47]	IHC staining levels of ER, PR, HER2 and Ki67	IHC	Prediction of recurrence risk in patients with ER + /HER2- breast cancer	Continuous recurrence score & risk classification (low, high)
Breast Cancer Index [48,49]	Combination of HOXB13/IL17BR ratio and Molecular Grade Index	mRNA quantification by RT-PCR	Prediction of recurrence risk in patients with ER + /HER2-, LN- breast cancer	Risk classification (low, high)
EndoPredict [50]	11 genes (proliferative and ER-related genes)	mRNA quantification by RT-PCR	Prediction of recurrence risk in patients with ER + /HER2-, LN + /LN- breast cancer	Risk classification (low, high)

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; LN, lymph node; mRNA, messenger ribonucleic acid; RT-PCR, reverse transcription polymerase chain reaction.

nodal status, tumor size, grade and age into a continuous score [62]. The CTS5 was developed in the ATAC trial and validated in the BIG 1-98 study, where postmenopausal patients received 5 years of endocrine therapy. The distant recurrence risk in years 5–10 was 3.0% for low-risk patients, 7.3% for those with intermediate risk, and 18.9% for high-risk patients.

Although several clinicopathological parameters and multigene assays are prognostic for late recurrence, this does not imply that patients with a high estimated risk will benefit from extended endocrine therapy. Only the Breast Cancer Index has been investigated in this context. In a cohort of 249 patients participating in the MA.17R trial, the distant recurrence rate was 16.5% lower in patients with high H/I-expressing tumors treated with extended letrozole compared to placebo [63]. However, thus far the predictive value of the Breast Cancer Index has not been validated. Current guidelines do not recommend the use of multigene assays in the decision-making on extended endocrine therapy [64,65].

Higher expression of estrogen-responsive genes is associated with a higher risk of late recurrence

More insight into late recurrence biology could improve patient selection for extended endocrine therapy. Therefore, we performed a retrospective pooled analysis to gain insight into biological pathways associated with an increased early or late recurrence risk. We collected publicly available mRNA profiles of 2231 primary ER-positive/HER2-negative breast tumors as previously described [66]. Patient characteristics are provided in Supplementary Table 1. Associations with early recurrence were studied in all patients with censoring at 5 years if no event occurred < 5 years after diagnosis. To study associations with late recurrence, we defined a second set that contained patients with a follow-up ≥ 5 years and no event < 5 years after diagnosis (Fig. 2). We ranked genes according to their association with recurrence-free survival, defined as time of diagnosis to local recurrence or distant metastasis, as determined with Cox regression analysis. Next, we performed Gene Set Enrichment analysis with the Hallmark collection from the Molecular Signatures Database [67]. A positive normalized enrichment score (NES) represented an association between higher expression of genes in a gene set with a lower recurrence risk. A negative NES represented an association of higher expression of genes in a gene set with an increased recurrence risk. Methods are described in more detail in Supplementary Methods. Results of the Cox regression analysis of individual gene expression with recurrence-free survival are provided in Supplementary File 1. NESs for all Hallmark gene sets are provided in Supplementary File 2.

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ctrv.2018.07.015.

In all patients, the largest shift in the association for early recurrence and late recurrence was observed for the 'estrogen response late' gene set. This gene set contains estrogen-responsive genes that were identified by comparing gene expression in estradiol-treated and untreated ER-positive breast cancer cell lines. Higher expression of these estrogen-responsive genes was associated with a lower early recurrence risk (NES = 1.89), but an increased late recurrence risk (NES = −4.79).

When we corrected for age, grade, tumor size, nodal status and systemic treatment, in all patients, higher expression of genes in the 'estrogen response late' gene set remained associated with a lower early recurrence risk (NES = 2.23) and a higher late recurrence risk (NES = −3.47) (Fig. 3). In patients who had not received any systemic treatment (*i.e.* no chemotherapy or endocrine therapy, n = 497), higher expression of genes in the 'estrogen response late' gene set was associated with an increased early recurrence risk (NES = −1.06), although not significantly, and an increased late recurrence risk (NES = −1.90). In contrast, in patients who had received 5 years of endocrine therapy only (n = 591), higher expression of these genes was associated with a lower early recurrence risk (NES = 1.58), while it remained associated with an increased late recurrence risk (NES = −2.72).

This pooled analysis shows that patients with higher expression of estrogen-responsive genes in the primary tumor who did not receive systemic treatment had a high recurrence risk persisting beyond 5 years. While 5 years of endocrine therapy reduced the risk for early recurrence in these patients, the late recurrence risk remained. This indicates that patients with higher expression of estrogen-responsive genes might benefit from extended endocrine therapy.

Discussion

Our review of clinical trials on extended endocrine therapy shows that the benefit of extended therapy on late recurrence is small. Although several tools are prognostic for late recurrence, selection tools for benefit from extended endocrine therapy are sparse. In clinical practice, patient selection for extended endocrine therapy therefore remains problematic.

Our pooled analysis suggests that late recurrences of tumors with high expression of estrogen-responsive genes are likely ER-driven. Long-term intervention in this pathway with extended endocrine therapy might reduce late recurrences in patients with these breast cancers. Previously, it was shown that patients with highly proliferative tumors and high ER-related gene expression had an increased risk for late recurrence [59]. ER-related gene expression alone was only

Table 3
Studies assessing the prognostic value of multigene assays for late recurrence independent from clinicopathological parameters.

Study	Population	Assay	Prognostic value for late recurrence	*P*
Sestak et al. [42]	TransATAC trial n = 940 ER+, LN+ and LN− Postmenopausal 5 years of ET	Prosigna Oncotype DX IHC4	LR χ^2 = 16.29 LR χ^2 = 5.55 LR χ^2 = 7.41	< .001 .02 .007
Sgroi et al. [51]	TransATAC trial n = 665 ER+, LN− Postmenopausal 5 years of ET	Breast Cancer Index Oncotype DX IHC4	LR χ^2 = 7.97 LR χ^2 = 0.48 LR χ^2 = 1.59	.005 .47 .20
Buus et al. [52]	TransATAC trial n = 820 HR+/HER2−, LN+ and LN− Postmenopausal 5 years of ET	EndoPredict EPclin Oncotype DX	LR χ^2 = 9.8 LR χ^2 = 9.9 LR χ^2 = 2.3	.002 .002 .13
Sestak et al. [53]	TransATAC trial n = 535 HR+/HER2−, LN− Postmenopausal 5 years of ET TransATAC trial n = 154 HR+/HER2−, LN+ Postmenopausal 5 years of ET	IHC4 Breast Cancer Index Oncotype DX Prosigna EPclin IHC4 Breast Cancer Index Oncotype DX Prosigna EPclin	LR χ^2 = 3.3 LR χ^2 = 11.2* LR χ^2 = 1.9 LR χ^2 = 18.4* LR χ^2 = 10.3* LR χ^2 = 0.8 LR χ^2 = 4.6* LR χ^2 = 0.7 LR χ^2 = 3.3 LR χ^2 = 6.1*	NA NA NA NA NA NA NA NA NA NA
Filipits et al. [54]	ABCSG-8 n = 1246 HR+, LN+ and LN− Postmenopausal 5 years of ET	Prosigna	LR χ^2 = 15.3	< .001
Sestak et al. [55]	ABCSG-8/TransATAC n = 2137 HR+, LN+ and LN− Postmenopausal 5 years of ET	Prosigna	HR 2.07 (95% CI 1.63–2.64)	< .001
Zhang et al. [56]	Stockholm trial n = 285 ER+, LN− Pre- and postmenopausal Tamoxifen-treated Multi-institutional cohort n = 312 ER+, LN− Pre- and postmenopausal Tamoxifen-treated	Breast Cancer Index Breast Cancer Index	HR 3.50 (95% CI 1.09–11.21) HR 9.24 (95% CI 2.85–30.00)	< .001 < .001
Dubsky et al. [57]	ABCSG-6/ABCSG-8 n = 1702 ER+/HER2−, LN+ and LN− Postmenopausal 5 years of ET	Endopredict	HR 1.28 (95% CI 1.10–1.48)	.001
Zhang et al. [58]	Massachusetts General Hospital cohort n = 402 HR+, LN+ (1–3 nodes) Pre and postmenopausal ET +/− chemotherapy	Breast Cancer Index (with tumor size and grade)	HR 1.41 (95% CI 1.06–1.89)	.02

CI, confidence interval; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR +, hormone receptor-positive; LN, lymph node; LR, likelihood ratio.
* $P < .05$.

assessed in univariate analysis, which revealed that high expression was associated with a low early distant recurrence risk, and no association was found with late distant recurrence in patients who received 5 years of tamoxifen and patients who received no systemic treatment. This is in contrast to our pooled analysis and might be explained by the fact that we corrected for relevant clinicopathological variables. Also, we only included patients with HER2-negative disease. Other studies have shown an increased risk for late recurrence in patients with tumors showing high ER-related gene expression who were treated with 5 years of endocrine therapy but it remained unknown whether this risk could be reduced by extended endocrine therapy [60,61]. Our pooled analysis showed that patients with higher expression of estrogen-responsive genes have increased late recurrence risk and, importantly, that this increased risk might be reduced by extending endocrine therapy.

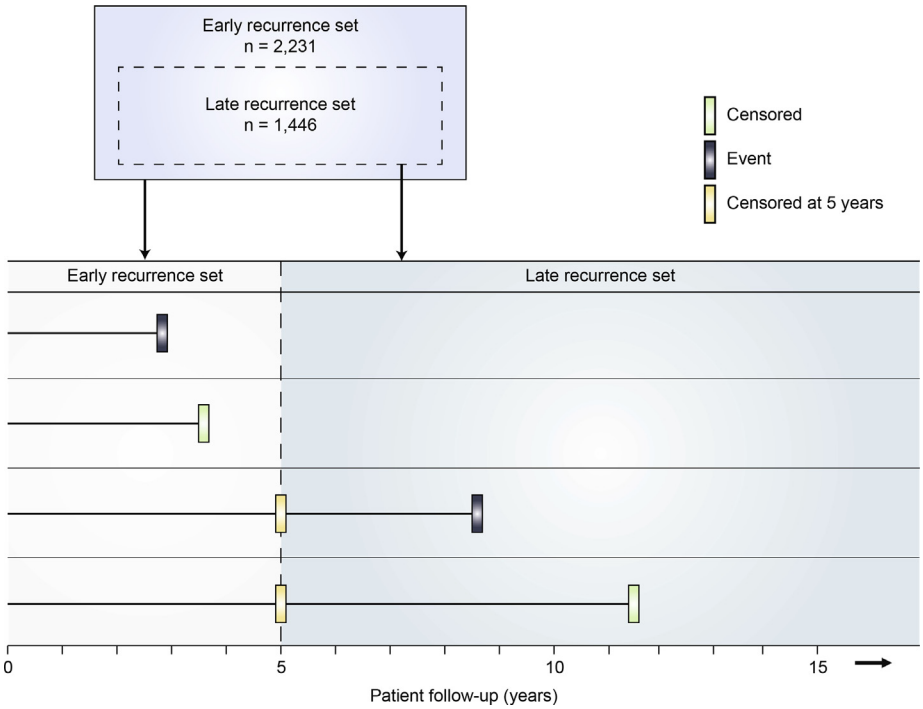

Fig. 2. Definition of early and late recurrence patient sets. For the early recurrence set, patients with a follow-up ≥ 5 years were censored at 5 years. For the late recurrence set, patients with a follow-up < 5 years were excluded. For each set, univariate and multivariate Cox regression analysis was performed to assess associations of individual gene expression with recurrence-free survival. Next, genes were ranked according to their association with recurrence-free survival and Gene Set Enrichment Analysis was performed on the ranked gene lists.

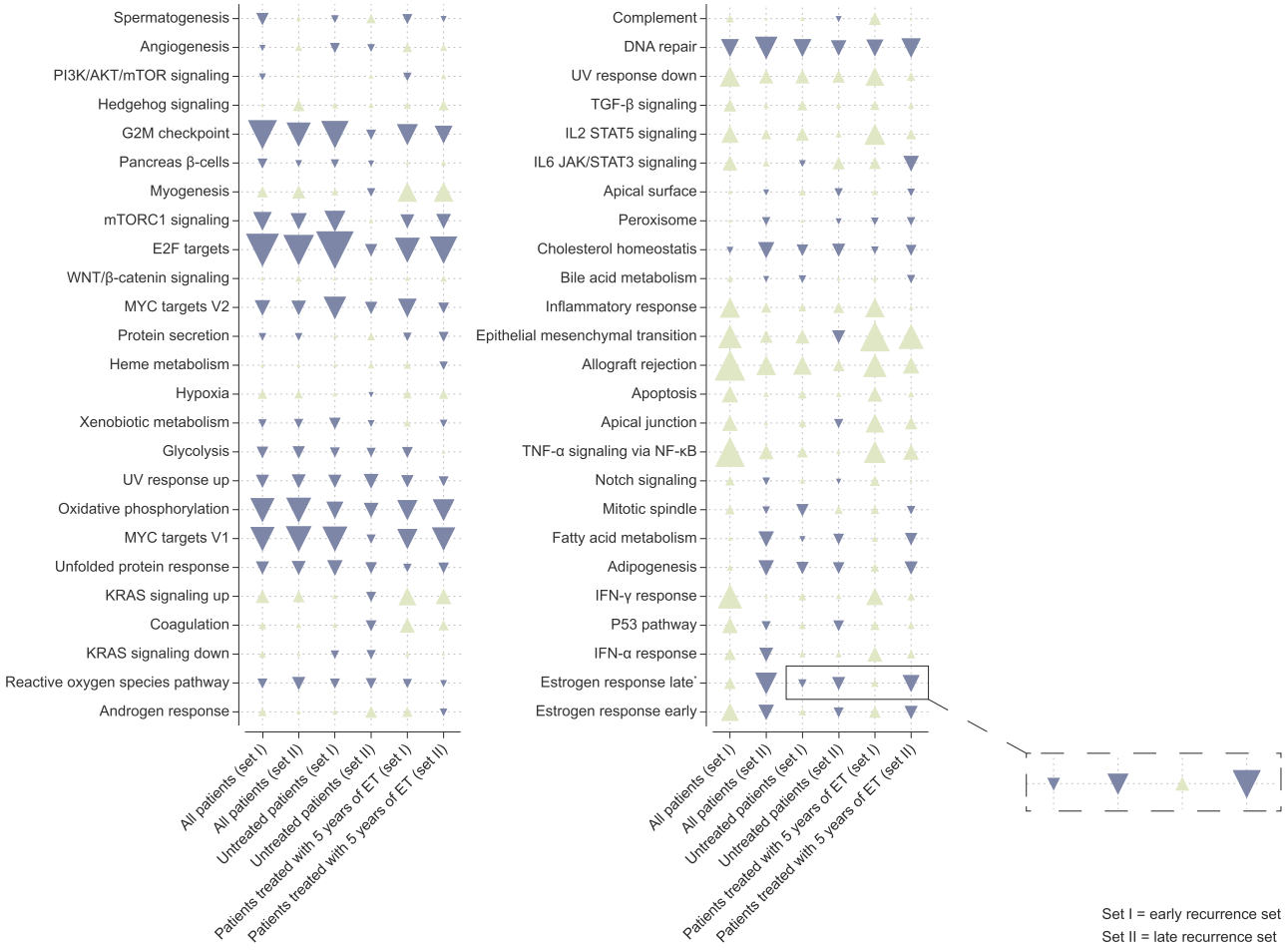

Fig. 3. Gene set enrichment analysis in early and late recurrence patient sets. Gene Set Enrichment Analysis was performed on ranked gene lists based on their association with recurrence-free survival. A green triangle indicates that higher expression of genes in a gene set was associated with a lower risk for recurrence. A blue triangle indicates that higher expression of genes in a gene set was associated with higher risk for recurrence. The size of the triangle represents the normalized enrichment score (NES). The insert shows the NES scores for the gene set 'estrogen response late' for the risk of early and late recurrence in patients who had received 5 years of endocrine therapy only and patients who had received no systemic treatment. ET, endocrine therapy. *Contains estrogen-responsive genes that were identified by comparing gene expression in estradiol-treated and untreated estrogen receptor-positive breast cancer cell lines.

Although extended endocrine therapy beyond 5 years reduces late recurrence risk in some patients, others still relapse. For these patients, alternative treatment approaches are warranted. In this context, several clinical trials are currently assessing the effect of combining endocrine therapy with CDK-inhibitors (NCT03078751, NCT02513394, NCT03081234) or mTOR-inhibitors (NCT01674140). Other potential strategies include developing agents capable of eradicating dormant DTCs or finding ways to keep these cells in a dormant state indefinitely. However, no actionable targets have yet been identified [68].

In conclusion, extending endocrine therapy to reduce late recurrence risk in patients with ER-positive breast cancer seems to benefit only a subset of patients. Identification of these patients remains a challenge given the few predictive biomarkers for extended endocrine therapy. We show that patients with higher expression of estrogen-responsive genes in the primary tumor have an increased late recurrence risk and that these patients might benefit most from extended endocrine therapy.

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Conflicts of interest

Elisabeth G.E. de Vries reports consulting/advisory board fees from Synthon, Pfizer and Sanofi, and grants from Novartis, Amgen, Roche/Genentech, Regeneron, Chugai, Synthon, AstraZeneca, Radius Health, CytomX Therapeutics and Nordic Nanovector, all unrelated to the submitted work.

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